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Sent by e-mail only:XXXXXXXXXX

Sanofi

Friday 12 July 2024

Dear Sir or Madam,

**Re: Final Draft Guidance — Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID4067]**

Thank you for your letter of 4 July 2024, lodging an appeal against the above Final Draft Guidance (FDG). Dr Chakravarty is temporarily unavailable and so in accordance with paragraph 3.1 of NICE's Guide to the technology appraisal and highly specialised technologies appeal process, I am conducting initial scrutiny on this occasion.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to provide an initial view on whether they are within the permitted grounds of appeal ("valid") and are at least arguable. The permitted grounds of appeal are:

* 1(a) NICE has failed to act fairly, or
* 1(b) NICE has exceeded powers;
* (2) the recommendation is unreasonable in the light of the evidence submitted to NICE.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information, are arguable, and fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn.

***Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly***

# Appeal point 1(a).1: There is no indication that the Appraisal Committee understood that applying NICE’s standard methodology means that isatuximab cannot be cost effective even at zero price

I am not minded to refer this appeal point to the Appeal Panel.

It is my initial view that the Committee did understand that applying the standard methodology would lead to a negative recommendation, even at zero price for isatuximab. In paragraph 3.17 of the FDG the Committee acknowledges your concerns that isatuximab plus pomalidomide and dexamethasone *"was unlikely to be cost effective even if it was offered for free"* and your request for the Committee to take a flexible approach. The committee refers to paragraph 4.4.16 of the Manual noting that it "*may consider a non-reference-case analysis with the background care costs removed if the NHS is currently providing care that is expensive or would not be considered cost effective"* and agreed to consider the analyses that were presented. This would suggest that the committee were aware of the challenges to cost-effectiveness and the consequences of applying the standard methodology.

I note that the Committee's approach to flexibility is covered by appeal point 1(a).3, which I am minded to refer to the Appeal Panel.

# Appeal point 1(a).2: NICE and the Appraisal Committee have not explained how, if at all, they have taken into account the fact that elements of the combination and comparators were appraised under NICE’s previous methodology, subject to a higher ICER threshold

I am minded to refer this appeal point to the Appeal Panel.

In reaching this view I consider it an arguable point as to whether the Committee has adequately explained how it took account of the different appraisal methodology applicable to elements of the combination and comparators.

# Appeal point 1(a).3: NICE’s proposed discontinuation of the appraisal rather than consideration of a flexible approach to its standard methodology was unfair

I am minded to refer this appeal point to the Appeal Panel.

In reaching this view I agree that there is an arguable point as to whether the Committee has fairly considered the application of flexibility to the standard appraisal methodology, in circumstances where elements of the combination and comparators were appraised under NICE's previous methodology. Whilst there is potential overlap between this appeal point and appeal point 1(a)2, my initial view is that they amount to discrete points that should both be considered by the Appeal Panel, with 1(a)2 covering the Committee's explanation of how it took into account the different applicable appraisal methodologies, and 1(a)3 covering the Committee's consideration of the application of flexibility to its own appraisal methodology.

I am of the initial view that the Committee's proposal to discontinue the appraisal does not, of itself, present an arguable point. Discontinuation was proposed rather than imposed, and in the absence of agreement from the Company, the evaluation proceeded. In the circumstances I cannot currently see any arguable basis for appeal on this point

# Appeal point 1(a).4: NICE’s refusal to refer isatuximab for commercial negotiation was inadequately explained and deprived Sanofi of the possibility to reach a satisfactory outcome to this appraisal

I am minded to refer this appeal point to the Appeal Panel.

In reaching this view I consider it an arguable point whether the Committee have provided an adequate explanation for why a commercial negotiation was refused.

# Appeal point 1(a).5: The Appraisal Committee failed adequately to consider the non-reference case analyses submitted by Sanofi

I am minded to refer this appeal point to the Appeal Panel, in respect of the challenge to the Committee's decision not to consider value attribution (discussed in numbered paragraph 3 below). I am not minded to refer the remainder of this appeal point to the Appeal Panel.

I understand this appeal point argues that the Committee took the following three decisions unfairly:

1. The Committee's decision to reject a non-reference case approach proposed by the Company that would involve removing pomalidomide and dexamethasone costs from the combination therapy arm. This is covered by appeal point 1(a)6, which I am minded to refer to the appeal panel. I cannot see any additional points here requiring referral as a discrete appeal point.
2. The Committee's decision not to consider generic pomalidomide prices expected to follow patent expiry later in 2024.

The Committee is required to use pricing that reflects as closely as possible the prices that are paid in the NHS (Paragraph 4.4.4 of the Manual). The Committee can only consider evidence that is presented to it at the time of the appraisal and the Committee is not required to look at future pricing. In fact, in this case, the Committee does appear to have taken a flexible approach. I note at paragraph 3.17 of the FDG that, '*after consultation the committee considered scenarios presented by the company that included potential discounts for generic pomalidomide*.' Following consideration of the scenarios '*It concluded that these suggested that introducing generic pomalidomide would not result in cost-effectiveness estimates for isatuximab plus pomalidomide and dexamethasone that would fall within the range that NICE would consider acceptable*.'

My initial view is therefore that whilst the Committee was not required to consider the future generic pricing, it has in fact done so in this case, and that the Committee's approach cannot therefore be arguably unfair in this regard. I note that no ground 2 (reasonableness) challenge is made to the Committee's conclusion that there was uncertainty around the timing of generic pricing becoming available and that in any event it would not result in cost-effectiveness.

1. The committee's decision not to consider value attribution, on the basis that NICE does not have a method for doing so.

At Paragraph 3.17 of the FDG the committee confirms that *'it considered the evidence and found it informative for context. But without a framework to consider this approach, the committee concluded that it was unable to consider value attribution in its decision making*.'

I am of the initial view that it was arguably unfair for the Committee to conclude that it could not consider value attribution in the absence of a framework for doing so.

# Appeal point 1(a).6: The Appraisal Committee’s conclusion that it is unable to base its decision on removing the costs of pomalidomide and dexamethasone, because NICE

**recommends these products as cost effective misinterprets the Manual and improperly fetters its own discretion**

I am minded to refer this appeal point to the Appeal Panel.

I note that in practice there is likely to be considerable overlap in the consideration of this appeal point and 1(a)3, since both derive from the evaluation methodology used for pomalidomide and dexamethasone, and this appeal point provides an example of flexibility that the Committee might have applied, the absence of which is challenged under appeal point 1(a)3. For that reason, I anticipate that the Appeal Panel may wish to consider these points together.

***Ground 2: the recommendation is unreasonable in the light of the evidence submitted to NIC***

# Appeal point 2.1: The Appraisal Committee’s conclusion that a standard reference case analysis should be used for decision making disregards the particular circumstances of this appraisal and results in an outcome that is perverse

I am not minded to refer this appeal point to the Appeal Panel.

I understand your point to argue that the decision to use the reference case analysis rather than the non-scenario analysis has resulted in an outcome that is perverse and therefore unreasonable.

I accept there is an arguable point that the committee may not have applied enough flexibility to the process, which could be considered procedurally unfair. This has been referred under appeal point 1a.3. I do not agree that, having done so, the Committee's conclusion is also arguably unreasonable.

A recommendation is not unreasonable simply because some other view is also tenable, even if the other view is “better” in some way. Provided the Committee’s conclusions informing the recommendation can be held reasonably then they are reasonable. The Committee has provided a detailed explanation for its conclusion at paragraph 3.17 of the FDG. The fairness of the Committee's approach to its decision-making will be considered under appeal point 1a.3 and 1a.6 but in reaching this conclusion the Committee has demonstrated a logical consideration of the evidence and my initial view is that it cannot be said to be arguably unreasonable.

# Appeal point 2.2: The inconsistent approach to modelling effectiveness of daratumumab is unreasonable

I am minded to refer this appeal point to the Appeal Panel.

In reaching this view I consider it arguably unreasonable for the Committee to choose a different model for overall survival to appraisal TA783 in the absence of new evidence to justify the different approach.

# Appeal point 2.3: The Committee’s approach to comparing the efficacy of isatuximab in combination with pomalidomide and dexamethasone does not reflect the evidence available and is therefore unreasonable

I am not minded to refer this appeal point to the Appeal Panel.

The Committee has set out their consideration of the evidence at paragraph 3.5 of the FDG. The Committee accepts there is a difference of opinion, and explains that it has a preference for the ICARIA- MM data. The Committee explains that it accepts the EAG's analysis that the SACT data presents an overestimate of the relative treatment effect and that it considers that the ICARIA-MM *'provided a more*

*robust estimate of relative effect*.' I am of the initial view that the Committee has demonstrated careful consideration of the evidence before reaching a conclusion.

In your appeal letter you note that Myeloma UK countered the EAG suggestion that patients who received isatuximab in combination might have been fitter than patients who received pomalidomide and dexamethasone and that the exclusion of patients who may have received pomalidomide and dexamethasone after receiving a treatment available on the CDF might have excluded the fittest patients. Whilst I acknowledge the reasoned opinion of Myeloma UK, where there is conflicting evidence it is not unreasonable for the Committee to select one view over another. Similarly, you argue that the Committee has placed too much reliance on the evidence of one expert. I do not consider this approach to be arguably unreasonable and note the Committee is free to take account of expert evidence which they consider to be most appropriate.

# Appeal point 2.4: The Committee’s conclusion that the early survival benefit for isatuximab in combination demonstrated in the SACT datasets is not plausible disregards consistent evidence from the ICARIA-MM trial and is therefore unreasonable

I am minded to refer this appeal point to the Appeal Panel.

In reaching this view I anticipate that the Appeal Panel will wish to explore the Committee's reasons for its conclusions in relation to evidence on this point from the ICARIA-MM trial.

# Appeal point 2.5: The inconsistent approach to assessment of utilities adopted in this appraisal relative to TA658 is unreasonable based on the evidence available

I am not minded to refer this appeal point to the Appeal Panel.

The Committee provides a detailed consideration of utility values at paragraph 3.12 of the FDG. The Committee acknowledges the approach taken in TA658 and explains why it prefers the approach taken by the EAG. The Committee explains clearly that it is also satisfied that the EAG model is simpler and a better statistical fit to the utility data from ICARIA-MM. The Committee appears to have reached its conclusion following careful consideration of the relevant evidence, including the approach taken in TA658, and I am of the initial view that its approach to the evidence is not arguably unreasonable.

Conclusion

The above sets out above my initial views on all of your appeal points.

In respect of your points which I am not minded to refer on you are entitled to submit further clarification and/or evidence to me within the next 10 working days, and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held which will be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information please ensure you have provided a version with this information redacted by 1 August 2024.

Ordinarily appeals are conducted on the basis of the appellants’ written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be

before the panel that you would wish to rely on you must let the NICE Appeal team know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than 2 September 2024. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Yours sincerely

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Sharmila Nebhrajani OBE

Non-Executive Director & Chairman

National Institute for Health and Care Excellence